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EDITORIAL

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful. The editor, alone, is responsible for their type, their tone and their tenor.

PRE-PROFESSIONAL EDUCATION IN PENNSYLVANIA

IN Pennsylvania we are justly proud of our secondary school program as applied to some phases of preparation for life service. Take for instance in Agricola's specialty, Agriculture. If a man wishes to raise a pig or build a pig sty, go into the poultry business and raise hops, as a side issue, he is required to pursue a very definite program in high school. He must study feeds, fertilizer, and fruits; markets, money, and materials; mathematics, science, and economics, with some attention to civics and English and many other useful studies. So important is all this preliminary preparation that special financial aid is given in support of the program, and special persons are employed in an official capacity to go among the pupils to see that the program is strictly followed. Not an egg can be hatched, or a peach ripened, or a cow dehorned unless this secondary school program is strictly carried out.

Everything seems to go well with a properly trained farmer until his horse or cow gets sick. He must then call in the veterinary man, for whom no specific training or preliminary, basic preparation is either expected or provided. By some mysterious working of the laws of nature not yet known, this veterinary person without guidance or appropriate curriculum is expected to transform his eyes into X-ray machines that look right inside that cow, for cows cannot talk, and the only sound they do make is the same whether they are sick or well, in love or in distress or both, hungry or only dry. Withal the veterinary doctor is expected to diagnose her trouble, prescribe the proper treatment, and restore her to health, so that the farmer can again profit by her existence. Is it not strange that the status of a healthy cow requires the special training of her caretaker but the sick cow is in charge of one who gets less from the State than does the inmate of a penitentiary? Special education is greatly em-

phasized where least necessary and considered worthless where it is most needed.

The farmer, as stated before, must follow a specific program of studies in high school to make him efficient, but when his mule cannot stand his abuse because his master has a thumping toothache, the farmer is compelled to go into the market places and seek out a dentist. The farm is at a standstill while the dentist does his stuff. But is it not strange that the dentist who is so necessary in this woolly, measly, economic world, needs no special high school preparation for the big responsibility he must ultimately carry? Apparently it has been discovered that vocations requiring the greater intellect succeed best when their educational background is zero. The amazing thing, however, in the making of a farmer and a doctor, or veterinarian or a dentist or pharmacist is that the farmer is quite proficient with only his well organized high school course but these professional persons must spend at least four years in college, after marking time for four years in high school until they reach the age when a college will admit them. Note that this admission to college is on age and not apparently on previous preparation or intelligence.

Space does not permit a further comparison between Agricultural Education and Professional Education, so let us now turn to the girl who is to be changed from a canned bean cook to a culinary expert.

The young lady in home economics education must hew to a strict nonelastic program of studies in high school. Religious observance is required to stitching, hemming and basting—both with thread and grease, also to canning, vitamins and calories and to all the category of allied and associated studies, under the watchful care of a specially subsidized teacher who keeps one eye on her in school and the other on her in her home to see that the program of studies is fully completed. She is now ready, let us say, to marry a pharmacist who is required by law and to know intimately ingredients of all kinds, tonic and toxic, and how to mix and compound them into an elixir of life or a witch's brew of death; the difference often being only the fraction of a grain. But this pharmacist according to our present puerile pedagogic premises does not need any specific training in high school for his start. He just naturally acquires the ambition to make concoctions like a native of Borneo learns to speak by thumping on a hollow log.

Our daughter can become a fine cook with only a high school education. She is master of the latest table and serving etiquette as well as of the science of dirtying every dish in the house for mother to wash, and pile up living expenses until father has to mortgage his house to pay his income tax. But the pharmacist to be needs nothing in particular while in high school. He just has to go to a high school technical or otherwise for four years, get certain numerical credits, after which he is ready for release to a high grade college which thus starts not with a balanced prepared freshman but with a hazard and a real handicap. If it were not just for the name of the thing he could save four years by not going to high school at all, and do his preparatory studying at home where he would more than likely use better judgment in preparation than do his present teachers in carpentry and mechanics.

How odd that a definite and well balanced high school program is so essential in the home economics field, and so haphazard, disjointed, unappropriate, and unessential to the pharmacist who by a drop of liquid, not of the hangman's trap door, holds the power of life or death over his home economics trained wife? It is truly marvelous how our educational process works.

Much more remains to be said on the difference between Home Economics Education and incomprehensible Professional Education but the fact that elaborate preparation for home economics classes is becoming compulsory in every district, rich or bankrupt, and technical high school graduates are still going to professional schools should be sufficient to show that our scrupulous attention to the high school training of the former group and its complete absence for the latter is deplorable and unreasonable.

Let us see the picture of the industrialist as compared with the professional practitioner. The pupil who aspires to an industrial career is given a well balanced high school curriculum, to train him in the skills necessary for success when dealing with inanimate machines and gadgets. He must complete special assignments in shop, with their related courses in mathematics, science, and commerce; be able to distinguish between cake cutters and bird houses, and with brace and bit, saw, hammer, and chisel, under the watchful eye of a specially subsidized teacher, a field agent and in a well equipped shop, learn the art and science in the construction, renovation and repair of inanimate structures in wood,—wooden heads excluded—iron and brass. In this process if a piece of wood, steel

or copper is marred it is of little moment as these things have no feeling and the supply of other parts is near at hand.

The doctor, pharmacist, dentist and nurse also deal with machines—human ones,—where a badly handled broken part may easily result in a maimed and pitiful existence for the remaining years of life, but for some justifiable reason, not safe to be revealed to the public, those who must know the scientific workings of the human body are expected to acquire their skills by pursuing anything, mostly unrelated courses in high school, and are left to shift for themselves in their endeavor to master the technique of handling so mysterious a creation as a human body. The spectacular achievements in the healing arts are marvelous when unhampered by educational preliminaries. After all there is justification for the attention to systematic education of the one group and its absence in the other, for there is evidence that in ancient times the brace and bit and chisel were used to bore holes in peoples' skulls to relieve headaches and other ailments, and it may be that history will repeat itself by again placing the mechanic in charge of the human machine, and the doctor to run the lathe and trip hammer. A rebirth of an age of miracles may be in the offing.

It is essential that to practice in the field of industry one must know the laws of physics and the rules in mathematics, but the optometrist who may restore sight or create blindness by the use of the very same laws and rules is not expected to master them in high school. It is confusing just how skills are acquired anyway, but apparently professional people need not worry over this perplexity, —it is not expected of them.

We come now to the field of business education. The girl who would aspire to an office appointment, must pursue a strict, exacting program in high school to master the technique of keeping intricate systems of books so as always to show the firm in the red and thus evade the honor of paying taxes. She is timed in her achievements, and must be familiar with all the latest devices necessary to a well managed office, even to the art of dress, use of cosmetics, and other evidences of refinement. Of course, as a rule the most recently trained ones cannot spell or construct words into sentences and paragraphs, but this is of minor importance as professional people don't have to know these things either. But is it not remarkable that an office trained girl must be required to pursue certain specified courses to properly equip her for her job, whereas a nurse or an accountant or

a chiropodist can learn to analyze their customers, trim them and relieve them literally and figuratively—the preceding word is, here, derived from figure, meaning money—on the basis of pursuing anything whatsoever that appears as a course in high school.

The undertaker was not intentionally omitted from this discussion. He is required at least to be a high school graduate but since he deals only with the dead, it is immaterial to them whether or not the undertaker had a specialized education. Just a reference to the agriculturist and undertaker: We are told that the farmers must avoid great excitement among their chickens as this reduces the egg crop, also cattle must be pampered and their whims catered to, even to providing classical music at milking time as this increases the yield of milk and cream—consumers do not know what becomes of the cream but they can vouch for the abundance of skim milk. For this the farmer must have a specialized high school course. The undertaker, however, needs to give no concern to the feelings of the widow or motherless child as he deals only with the dead and since his charges are fixed, requiring no figuring such as is necessary on the farm, any kind of high school work is sufficient just so the total is sixteen units under the old dispensation and twelve under the new dispensation.

A summary of all this shows that pupils who aspire to a career in the industrial field, business world, agriculture or home economics are provided with a fine, appropriate high school course by the State that eminently fits them to enter a higher institution for further education without any deficiency in studies, but on the other hand, anyone who aspires to a career in the professional field is given no aid whatsoever in high school to lay the foundation for subsequent preparation, and this is why hundreds of high school graduates who apply for admission to professional schools are not admitted as their high school course is found to be deficient in many basic and essential courses. There is justification for this procedure by the state, however, for we can boast of courses in agriculture, industrial education, business education second to none in the country, but being a big state and not wishing to be selfish at all we find it expedient to have the lowest pre-professional standards in the country.

As a reward for the State's indifference to basic preparation on the high school level for professional life, the professional would-be practitioners are required to pay fees ranging from $2.00 to $100.00

for the privilege of being compelled to display on their office walls a license which is to remind pupils in high school who desire to study medicine, dentistry, pharmacy, nursing, and the like, that they must not be too choicy in their selection of appropriate high school studies as this might have the effect of lessening their number of years of attendance in college to get ready to study their chosen profession. In the four other major fields of endeavor, definitely prepared high school programs are provided by the State and, therefore, it is not necessary that they should be especially taxed to secure a license to work at their vocation.

The professional group has the added distinction of volunteering to be forced to register every year to the tune of one to ten dollars *per,* just as a reminder that no particular attention should burden their minds when going to high school as to what or what not to study. This procedure does not seem on the surface to make sense—or does it? Since the State collects every two years more than one-half million dollars in fees from the professional group, maybe it does make sense to neglect their rights to an appropriate curriculum while in high school.

It is interesting to note that specific curricula are provided by the Department for the special fields of industrial education, business education, agriculture and home economics for which the school laws make no specific provision, while no curriculum is provided for professional education when the law requires that secondary school standards shall be maintained for professional study, and those preparing for the vocations of industry, business, agriculture, et cetera, are not required to secure a certificate for what they do have, while the professional group must by law secure a certificate for what they don't have. Truly this is an odd and erratic system.

A review of the entrance requirements to colleges and universities shows that they still maintain an appropriate and specified list of courses to be completed in high school by those preparing for professional schools, and it frequently occurs that *high school graduates* are given the honor of spending another year in high school, if they can get in, or in a private secondary school at a big expense to secure the necessary courses and backgrounds before they can either enter or continue their college course. The Department, which seems to have some official relations with and supervision over these colleges pays no attention to these required and appropriate courses in high school for those headed for college and professional life—or disaster.

The colleges are definitely cooperating with the professional schools in the appropriate training all along the line for the professional group, but the State which should be the leader of all of them apparently is cooperating with neither; the result of which is that school officials who now must bear the brunt of the reaction for these shortcomings in high school are clamoring for the maintenance at public expense of junior colleges in every city and town of any size so that these pupils may have the pleasure of spending two more years in a higher school to do in part at least what they shoud have done in high school. It is truly marvelous to observe that school officials who have never pursued a single course in a professional school and know nothing of the experiences, needs and problems of the professional practitioners, presume to determine exactly what it requires to become a doctor, a dentist, a nurse, *et cetera.*

In conclusion, it is emphasized that there is disaster to the cause of the professions if we continue to neglect to provide an appropriate high school course for future professional practitioners.

The Hypochlorites in War Surgery. W. Manninger. *Deut. med. Wochschr. 66,* 169 (1940) through *Squibb Abstr. Bull. 13,* 469 (1940). A combination of 5 cc. of sodium hypochlorite solution (Hydroxygenlauge) and 100 cc. of a saturated boric acid solution is 10 times as active a germicide against B subtilis as is calcium hypochlorite (Caporit) or other hypochlorite solutions. A 0.1 per cent. solution of Hydroxygenlauge with saturated solution of boric acid kills staphylococci and streptococci in 2 minutes. The proportion of boric acid in the mixture is sufficient to neutralize the excess alkali of the sodium hypochlorite and the combination is tolerated by the tissues even in 5 per cent. concentration. The undiluted mixture of 5 cc. of the first mentioned hypochlorite solution and 100 cc. of saturated boric acid is recommended for cleansing wounds while a 1:4 dilution of this mixture with boiled water is recommended for irrigation. The sodium hypochlorite preparation "Hydroxygenlauge" is a Hungarian product containing approximately 8 per cent. Cl and having a pH of about 8.3. The American sodium hypochlorite preparation "Antiformin" contains much less Cl and considerably more alkali.

The mixture of this particular sodium hypochlorite solution with boric acid solution has been termed "Hypnabor". It resembles Carrel-Dakin solution and it is much more readily prepared.

L. F. T.

ORIGINAL ARTICLES

GASTRO-INTESTINAL DERANGEMENT DURING DROUGHTS*

(with special reference to contaminants of vegetable origin)

By George G. Schaut**

THIS is a rather formidable title to use when thinking in terms of water supply. In nature there is very little virgin water, for as soon as it starts falling from the sky, water begins to take up certain substances from the atmosphere. Whatever mineral content it has when it reaches its destination has been acquired by contact with the soil. If a water dissolves the mineral matter from the soil, by the same token, some of the organic matter, chiefly vegetable, must likewise be taken up. Ordinarily the concentration of these substances is such as to be of little or no consequence as far as potability is concerned. Lack of rainfall and drought, together with natural evaporation undoubtedly concentrate the constituents in water.

This is especially made evident by the increase in hardness (greater soap consumption) and the greater color of natural bodies of water during droughts. A heavy rainfall during a long continued dry spell does not relieve drought conditions. It may actually carry vegetable matter, made more potent by drought into the main body of water, there to be concentrated by natural evaporation. Sunlight even is "the hand that rocks the cradle", for photosynthesis accounts for the luxuriant growth of substances in water and some of these are quite undesirable as far as a palatable, as well as, a potable supply is concerned. In a previous article, the author (1) showed that a vegetable substance in rather high concentration must have been present in a water supply. Some of the products herein mentioned could find their way into water courses, particularly in the fall season when trees and shrubs shed their leaves and during droughts the increased concentration of vegetable contaminants may become a health factor.

It is a well known fact that among men in Northwoods' lumber camps, well along toward the end of the summer or early fall when

*Synopsis of a paper presented on October 5, 1939, at the Four States Section Meeting of the American Water Works Association at Reading Pa.

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dry leaves and decayed vegetable matter gets into their water supply, there is usually a diarrhea epidemic among the members of the camp. As these men are usually hardy and their resistance should be great, still they easily fall prey to gastro-intestinal disturbances not of the bacillary type. The water has always been suspected as the causative agent, but since it occurred regularly every year and was more or less mild in nature, it has been always taken for granted and very little done about it.

The cause of diarrhea outbreaks during and following severe droughts in various sections of the country received much attention at the time they occurred. Little of a scientific nature was uncovered, only postulations where *anyone's guess was as good as another's.* Substances of more or less vegetable origin, that increase peristaltic action, have been known for a long time. One plant principle and its poisonous hydrolysis product were given to test animals through the medium of their drinking-water and this experimental work is herein recorded. Then follows a general discussion of the subject as it pertains to water and drought.

Two very common symptoms caused by most any poison, regardless of increased peristalsis are nausea and vomiting. Nausea and vomiting are nature's first line of defense and the next line of defense is diarrhea. In addition the following may also occur, headache, distention of stomach and bowels, pain in abdomen and/or bowels and even diarrhea with bloody stools. Some people believe that the poison in plants is part of nature's scheme for survival of the species.

The concentration of vegetable substances that would probably be encountered in water courses † and possibly cause intestinal disturbances limits the number to only the most potent. From experience with vegetable substances only those with a therapeutic value of 50 mg. or less per day should be given consideration. Any concentration above this will broaden the subject so as to include many more of which there is practically no end. The volume of water to be taken *per os* to make them effective would then be excessive for any one day and certainly could not be continued over a longer period.

The vegetable substances could be grouped according to the following chemical divisions; (1) alkaloids, (2) bitter principles and their related products, the resinoids, (3) toxalbumins, (4) glucosides

†The Editor relates a personal experience with large fish in a lily pond in his garden. When screened prior to the winter season the fish invariably survived the winter. But when leaves of the weeping willow were permitted to fall in the pond the fish would inevitably be poisoned.

including those that show cyanogenesis i.e., nitriles or organic cyanides.

Nitriles

Cushny (2) in his treatise on Pharmacology and Therapeutics states that nitriles are not so poisonous as cyanides but cause gastro-intestinal irritation—symptoms and action of cyanide poisoning—nausea and vomiting, pupils dilated, after unconsciousness then bowel evacuation. The central nervous system is first stimulated and then paralyzed. The fact is, that cyanogenetic glucosides are a complex form of nitriles. In a previous article (1) the writer established with some degree of certainty the presence of a nitrile (cyanogenetic glucoside) in a water supply. The glucoside very likely was mandelonitrile diglucose or what is commonly known as amygdalin. If not this, then at least some salt of the nitrile of formic acid, commonly called prussic acid with its salts—known as cyanides. The question of toxicity must be considered for both oral and injectable materials. A substance may be very toxic by injection into the blood stream or under the skin, but cause no harm when taken orally. The digestive forces break it down and when that occurs it can cause no harm, if of course, the degradation products are not harmful. In the case of amygdalin, it only becomes harmful to fish when they in turn have caused its hydrolysis with the production of cyanide.

Experimental

The chemical given to rats was placed in their drinking-water contained in inverted bottles with dropping tips to avoid concentration of the chemical due to evaporation. Experiments were conducted upon mature white rats, each having a separate cage. Four rats were given tap-water containing 10 p.p.m of amygdalin and at the same time another set of four rats was given 1 p.p.m. of NaCN. Those taking amygdalin gave perfectly normal, well formed stools during six consecutive days test time, while those taking NaCN produced unformed stools and in one case, watery. As these rat experiments were performed simultaneously, the one set acts as a control for the other.

At a little later date other female rats of mature stature and well formed, were given a ten-fold increase in the dosages of the respective chemicals during eight consecutive days. The stools of all the animals were of normal consistency and there was no tendency toward loose-

ness. This was again repeated at a later date and in addition to their drinking-water having the chemicals, each received 2 to 3 cc. per day *per os.* There was no indiction of diarrhea from either chemical. A few weeks later, water drawn directly from the laboratory tap containing free chlorine had the chemicals added and this water given to the rats. Here again, no diarrhea could be produced.

Animal experimentation, at its best, is more or less uncertain, for different species of the same animal may give entirely different reactions. Rimington (3) found with rabbits that amygdalin alone had no effect in doses as large as 0.5 gm. (given to 1900 gm. rabbit by stomach tube) corresponding to approximately 30 mg. of HCN, nearly three times the normal lethal dose. Even when a very active emulsin preparation was simultaneously administered, this quantity of glucoside was insufficient to produce death. Still, poisonous plants and especially of the cyanogenetic type are the bane of all cattle raisers in South Africa, and English scientists have given this problem a great deal of their time.

About a year later the animal experimentation was resumed using new rats and paired two male and two female in separate cages. Water containing 4 p.p.m. of NaCN, to which was added chlorine so as to satisfy the demand leaving only a residual chlorine of 0.05 p.p.m., was made fresh daily and given to them. In addition each received 2 to 3 cc. by pipette. During seven consecutive days this water did not in any way affect their stools.

About a month later a final run was made using new rats paired as just mentioned and their drinking-water consisted of only 2 p.p.m. of NaCN for seven days (made fresh daily) and during the first seven days, stools were normal. The water consumption was about normal for the animals. On the eighth day the concentration was stepped up to 10 p.p.m. of NaCN and continued for another week and toward the end of the week they developed definitely watery stools. When the water was changed to ordinary tap-water their stools became well formed again. This is the first confirmation of the run made a year ago when 1 p.p.m. of NaCN gave the same results. For testing chemicals by way of drinking-water in such low concentrations, it seems to the writer to be something to be valued, especially when obtaining a confirmation even if almost a year intervened. The food given to rats during all experiments was of normal character for this species of animal. The food intake by the rats in all the ex-

periments was fairly constant, so that their solid intake could not account for any change in stool consistency.

While the work with the rats was being done, it occurred to the author that perhaps, a meat eating animal should be used and the dog was chosen. Three dogs of the hound variety were obtained, one male dog of rather tall stature was placed in a separate cage and two female of low stature placed together in another cage. The three dogs were given drinking-water containing 5 p.p.m. of NaCN, made fresh daily using stabilized tap-water free from chlorine. The other factors in their daily routine were normal, even to being put out for supervised exercise. The dog of tall stature had a loose moist stool on the second day after drinking the water and developed a fluid discharge from its eyes. This dog was taken off this water and rested for a few days, and it became perfectly normal. Then the dog was put back on test again. The other two dogs of low stature were perfectly normal for a week but seemed to lose some vigor during the second week and during the third week all three dogs produced moist amorphous stools on alternate days only, whereas, the in-between days the stools were perfectly normal. Physiological action of this kind would seem to indicate that the concentration of cyanide is a threshold dose. After the third week, the work was discontinued and the dogs again gave perfectly normal stools. The phenomenon observed is certainly not that of diarrhea, although the stools were somewhat soft and mushy and not normal. The food intake in all dog experiments was fairly constant. There were eight other dogs in the animal-house during this time, all receiving the same food and daily routine as the dogs under test, with the exception, that the other dogs were not given anything but ordinary tap-water as their water intake. None of these dogs had moist amorphous stools. It is regretted that the peculiar conditions under which the experiments were conducted precluded a more detailed and lengthy study.

Amygdalin was not given to dogs, for its hydrolysis would only be an indication of the presence of the proper enzyme in the gastro-intestinal system and then any cyanide produced might give the same results as cyanide administered alone, provided that the liberated glucose does not counteract its toxic effect. Cyanogenetic glucosides are not quickly broken-down even though it is possible for the H-ions of the gastric juice to bring about some hydrolysis, in which case the liberated HCN is very small and not likely to be toxic. It is to be expected that the glucoside could readily pass all the way to the intes-

tinal tract, almost entirely undecomposed, and there be hydrolyzed, if the proper enzyme be present. The cyanide there formed might cause some intestinal irritation, or organic disorder. Witthaus (4) in reporting the work of other investigators, states that decomposition of amygdalin, with liberation of hydrocyanic acid, occurs in the intestine under the influence of the digestive enzymes.

Positive and especially negative results with test animals must be appraised with a great amount of reserve, for Woolpert and Dack (5) in the very beginning of their study of toxic substances from staphylococci came across the practical difficulty that none of the usual laboratory animals responded to oral administration of staphylococcic products. Filtrates of proved toxicity for man had been repeatedly fed in large amounts to rhesus monkeys without producing any visible effect.

The prolonged use of food (cassava, maize, peas, and beans) rich in "cyanic plants" by humans is best recorded by Clark (6, 7) in his study of body ailments among natives of West Africa. He found it to produce pellagra-like symptoms. He also gave a great amount of time to the experimental administration of cyanide and nitriles to animals and although, no mention is made of vomiting and diarrhea, nevertheless, liver disorder is produced by both substances in man and animals and gastro-intestinal derangement is not uncommon. James (8) in his work upon cyanides in urine, found that eating cabbage and Brussels sprouts greatly increased the amount of cyanogen as cyanide execreted by the person, with no mention of any ill effects. These cruciferous plants contain nitrogen as nitriles or hydrocyanic acid complexes.

Non-Fatal Cyanide Citations

Williams (9) describes several cases of non-fatal cyanide poisoning occurring among people who ate in hotels, due to cyanide silver polish, left on the cutlery. In all cases the symptoms were vomiting, abdominal pains and diarrhea. Symptoms usually came on about four to six hours after eating the meal. The examination of the evidence shows that the silverware was usually dipped in the cleaning solution. Then, it was said, the ware was rinsed in water. Even if the rinsing were omitted, the actual quantity of cyanide remaining on the ware would seem very small, in view of the fact that the solid cleaning preparation before use only analyzed about 20 per cent. cyanide. This only goes to show, that even a few milligrams of actual cyanide, lurk-

ing in the corner of some coffee server or between the tines of a fork, and then, what is more, taken with other food, can innocently be the cause of intestinal derangement of an unsuspected source.

Gettler and St. George (10) state that symptoms of chronic cyanide poisoning vary considerably with each person, nausea, headache, giddiness and scratching or irritation of the throat. Well developed chronic poisoning even produces vomiting. In a recent personal communication the senior author advised the writer that gastro-intestinal disturbances are even to be expected.

Souwers (11) reports a case of a photographer working with KCN, both in solid form and solution, developed among other symptoms, nausea, bowels obstinately constipated and then looseness alternately, shortness of breath and sweats. The alternate constipation and looseness of bowels is not unlike the phenomenon observed in the dogs (*loc. cit.*).

A Vegetable Extract

Couch (12) after a study of milksickness, called in the southwest "alkali disease", found that cattle that had been fed upon richweed or white snakeroot developed trembles and cows secrete poisonous milk. This weed *Eupatorium urticaefolium* Reich. is found throughout the eastern United States and even into the midwest. Outbreaks are most common in late summer, early autumn and especially during droughts when the cattle have been forced to graze upon it due to scanty other food. Poisonous butter during the winer, when richweed has been killed by frost has caused sickness. It was only after an exhaustive study that bacteria as a cause was finally ruled out. The substance responsible for this poisoning is an oily liquid called tremetol (not a nitrogenous compound). He does not believe that the temperature of pasteurization is sufficient to detoxicate it. Tremetol withstands temperature of boiling water. In large communities its presence is difficult to determine and its effects would ordinarily be passed off as food poisoning, gastritis or some other temporary intestinal disorder. No doubt, the water supply would be suspected and very likely condemned, particularly if unchlorinated and a few coliform organisms had been found. Marsh (13) *et al.* found tremetol in the rayless goldenrod *Aplopappus heterophyllus,* sometimes called "jimmyweed". In animals constipation was noted which may be preceded or followed by diarrhea and even hard bloody stools.

Toxins

Even coliform organisms are now known to form exotoxins and endotoxins. Minett (14) states that a strain of B. Coli from milk of a cow with actute mastitus caused vomiting, and enterotoxin from staphylococcus causing food poisoning was found to be resistant to heat of 95° C. for 30 minutes. Jordan *et al.* (15) showed with toxic staphylococcus filtrates put into milk and given to human subjects, that contact for 3 minutes with a rather strong dose of chlorine did not destroy the toxic property. It has been shown that some poisonous substances are not destroyed by chlorine and since coliform organisms produce toxins, so it is quite possible that a heavily polluted water when chlorinated may be free from coliform organisms and other bacteria, but the toxins may still be present to react in the human system. Perhaps bacteria decomposing dead fish in a stream form toxic products that produce the dysentery, i. e., similar to bacterial decomposition of meat; where even though the whole menstruum is sterilized the chemical products are sometimes extremely poisonous. Chlorine may kill the organism but what becomes of the cell contents—the toxins. No one discredits the fact that after the organism is "dead" the enzymes are still active and the cell is "alive" chemically.

Some investigators believe that toxins cannot react to produce bodily ailments when in the presence of chlorine, for the oxidation potential of chlorine is such that the toxins are inactivated. This is certainly not in agreement with the findings of Jordan *et al.* (*loc. cit.*). The fact that an oxidizing agent is present in a chemical system is no guarantee that a reducing agent cannot also be present, especially is this true in dilute solutions, such as are encountered in water. In a previous article the present author (1) showed that several vegetable substances and one inorganic reducing agent were not detoxicated by chlorine as far as fish are concerned. Also, one non-toxic reducing agent (KCNS) actually became very toxic to fish by chlorination. Enzymic activity as measured by the hydrolysis of amygdalin was also not destroyed by chlorine. Both chlorine and toxins are capable of existing in the same medium *per se* and whenever the chlorine (active) is destroyed or disappears as when drinking-water comes in contact with the oral membranes, saliva and also food; then the toxin may be in a position to exert its influence and cause a disturbance in the human system. Surely, the cry that chlorine in water destroys or affects the gastric juices of the stomach, and destroys the enzymic

activity necessary for the proper assimilation of food, appears to be founded upon a wish of those opposed to the use of chlorine in water treatment rather than facts.

Air-Borne Infection

The work of the Wells (16) on air-borne infection may some day be just as classical in that field of scientific endeavor as Pasteur's germ theory of disease was when applied to water. With the purification of air may come the answer to some of our so-called water-borne epidemics, especially those of very obscure origin as during drought periods. There is no doubt in the writer's mind, that certain individuals are allergic to some air-borne substances that act upon the gastro-intestinal tract.

Nelson (17) in a study of epidemics of diarrhea caused by *Cl. Welchii* in milk during the fall of the year, when natural increase of the acidifiers was lowest, was led to conclude that epidemics of anaerobic intestinal infection are far more numerous than are usually recognized. He also believed the same to be true during seasons of drought (1929-1931) when dust and dirt were most contributory to pollution, for dust always contains dry bacteria especially of the sporulating type, even though ordinarily, most of these are harmless to man. It is possible that under other climatic conditions the anaerobic forms are held in restraint by aerobic influences.

Drought Data

During the extreme drought period of 1930-1931 a number of cities using surface waters (rivers) as a source of water supply for their purification plants found that epidemics of gastro-intestinal disturbances were not uncommon. It was noted during the epidemic that boiling the drinking water prevented the illness and this was suggestive that a viable organism was responsible. The present writer found that gently boiling a cyanide solution containing 10 p.p.m. of sodium cyanide, in distilled water, for 15 minutes also destroyed the cyanide. When tap-water was substituted for the distilled water the cyanide could not be entirely destroyed by 15 minutes boiling but showed a reduction of about 50 per cent. Many dead fish were found in the waters at the time of the epidemics. At Louisville the Ohio River, though green and clear carried a very high algal and plankton content. At Charleston, W. Va., the organic matter, algae

and protozoa were extremely high. It was impossible to hold a residual chlorine in the water going to the consumers and the water had the characteristic "rivery" taste, better described by laboratory workers as moldy or musty. The chlorine demand of the raw water rose to 20 lb. per million gallons and at one time prechlorination was practiced with the dose of chlorine running as high as 4 p.p.m All are familiar with the fact, that even though the raw water carried a high coliform content, the water going to the consumers met the Treasury Department Standard.

Discussion

A systematic investigation of the sewage waters of the city of Pécs by Gyorgy Scheff (18) proved the existence of *Coli* bacteriophages during the whole year whereas the bacteriophages of typhoid fever and dysentery appeared only in the spring and fall. Perhaps the appearance of such bacteriophages in sewage will be an indication of coming epidemics. It seems to the writer that "phage" activity, enzymic activity, and the filterable viruses or self-reproducing enzymes are more or less closely related, for they at least have one property in common, in that all are inactivated by heat. This being the case then the detection of specific enzymic activity in water by chemical means may be an indication of on-coming epidemics. This may be only an *idle dream* of the writer and cannot be checked until drought and dysentery epidemics again occur.

Much has been said from time to time about making the bacteriological standard for drinking-water more rigid, i.e., testing water in larger volumes than 50 cc. (five 10 cc. portions). In the writer's mind larger inoculative portions are a waste of media and time together with the use of excessive numbers of glass apparatus and last but not least, the incubator space. Surely, if the standard for the finished water is made more rigid a corresponding fewer number of coliform organisms will be permitted in the raw water which means that the number of streams now suitable for water supply will necessarily be decreased or methods of purification will have to be greatly improved over what are now in use.

The author is of the opinion that a sterile, foul smelling and bad tasting water in itself could set up psychological stimuli that would cause gastro-intestinal disturbances. The actual chemical substances giving the water these properties could be present in even larger quantities and if the water were swallowed by means of a stomach

tube connected to a closed container so as to prevent the person from smelling or tasting this water, no gastro-intestinal disturbance would be produced. Organs are affected to some extent through nervous impulses whether brought about by actual substances or allergic reactions. The allergists tell us that the classical allergic reaction in the stomach and intestines is with either nausea or vomiting shortly after ingestion of the allergen or, if it is retained, diarrhea and even true mucus colitus after an interval of several hours. As the gastro-intestinal system and the respiratory system are connected by the largest nerve system in the human body, the vagus, it certainly takes very little stretch of the imagination to believe that a substance floating around in the air and inhaled might be allergic to the gastro-intestinal system even though the substance never reaches the stomach.

The factors emotion and idosyncrasy must not be overlooked. Even gastro-intestinal "upsets" of a psychical nature could be the cause of localized cases. How much diarrhea of an epidemic nature is to be traced to these, is not readily ascertained. On the other hand, a perfectly safe water, having a slight unusual odor and/or taste occasionally, can be the impetus for some people thinking and talking themselves into a sort of hysteria over this otherwise pristine fluid and before long the situation is like the snowball going down hill. One form of occasional diarrhea which comes down through the ages is that of the "internal blush," so-called by Alexander (19). His explanation is that a sudden nervous shock by causing vasodilation may send an excessive supply of arterial blood through the mesenteric arteries (in effect an "internal blush"), and cause secretion of water into the intestine (nervous diarrhea). This reaction is, in the writer's mind, also, the scientific explanation for sporadic outbreaks of diarrhea among workers in the heat of the summer, when, due to electric cooling, the drinking water has been found to be *too cold* for safe use. Even in winter time, in some localities, the faucet water may be 15 degrees colder than that of the average spring.

Summary

The presentation of some experimental evidence that the continuous administration of an alkali cyanide in sublethal concentration, through the medium of their drinking water during several days, caused a mild form of gastro-intestinal derangement in rats and dogs.

Alkali cyanide in a natural water was partially destroyed by boiling and completely eliminated by boiling when in distilled water.

Water containing chlorine is dechlorinated immediately in the oral cavity of humans.

Conclusion

It is a fact that organic cyanides (nitriles) are found in common foods like cabbage and Brussels sprouts; that sauerkraut, both raw and cooked, in rather generous helpings has always been considered an intestinal stimulant as well as a deranging agent to others. The fact that many investigators have used up to 10 mg. of NaCN upon human subjects both intravenously and orally for scientific investigations and apparently without ill effects would leave this an open question in the author's mind. Except that an injection now and then or a single dose orally is not to be compared to a continuous small dose *per os*. In the case of small continuous quantities, allergic as well as idiosyncratic reactions might be produced.

Allen (20) and Hering (21) in their *Materia Medica* give many references to cyanide in sublethal quantities producing vomiting and diarrhea. The writer wished to supplement this with some recent *first-hand* data and tried to produce the same symptoms in animals by a rather definite concentration in their drinking water. His custom of weighing experimental findings with great reserve does not even permit a final conclusion at this time. He feels that further work should be done by others on this important subject when drought again occurs to see if cyanide is present in drinking water and is common to all epidemics. It is to be recalled that the author only determined its presence in the raw water, not looking for it in our drinking water because there was no epidemic of intestinal disorders in our city at that time. It would be highly desirable to note the absence or presence, if possible, of a foreign protein poison, certain amines, ptomaines and last but not least certain vegetable substances herein mentioned. Then, and only then, would it be fair to draw a final conclusion, for all the pharmacological experiments using animals may only be a poor imitation of what actually takes place in humans.

The one cardinal feature lacking in the case of most diarrhea epidemics, especially those of the drought years, was the question as to whether they were of the bacillary type or not. To determine this is not the most pleasant and easiest of laboratory techniques, but it does seem to the writer as though the dogs of a community could be

of some help. Vaughan (22) showed with diazobenzol butyrate and tyrotoxicon that dogs do vomit and get diarrhea. It is a well known fact that dogs do not react to bacterial invasions as humans do. Therefore, if the dogs of a community show signs of diarrhea it is pretty certain that the dysentery is not of the bacillary type.

More emphasis should be given the chemical and physical nature of water, rather than so much agitation about increasing the bacteriological standards.

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An expression of deep appreciation for helpful advice and criticism during this work is due Dr. Ivor Griffith, Dean of the Philadelphia College of Pharmacy and Science, and Dr. Joseph S. Hepburn, Professor of Chemistry, Hahnemann Medical College, Philadelphia. Dr. Frank W. Konzelmann, Professor of Clinical Pathology, Temple University Medical School, Philadelphia, Pa. was most helpful, for under his direction the animal work was performed. The author is indeed very grateful to Seth M. Van Loan, Chief Engineer of the Water Bureau, for permission to present this paper. Those persons directly associated with the author at the laboratory were very helpful from time to time by offering many valuable suggestions.

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$$HO\ CH_2\ C(CH_3)_2\ CH\ (OH)\ CO\ NH\ CH_2\ CH_2\ COOH$$

Pantothenic acid belongs to the B complex and has been known as a "filtrate factor" and the "chick antidermatitis factor." This vitamin undoubtedly will be found of importance in animal nutrition and that it is required by all higher animals in general. L. B.

EFFECT OF INTRODUCTION OF THE HALOGENS INTO THE PHENOL MOLECULE ON TOXICITY TO GOLDFISH. I. MONOCHLOROPHENOLS

By W. A. Gersdorff and L. E. Smith

[Contribution from the Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture.]

Introduction

IN A systematic investigation of the effect on toxicity of slight chemical changes in composition of phenolic compounds, studies have been made with cresols (1), phenyl (2) and tolyl mercaptans (3), and nitrophenols (4). The introduction of the methyl group into the phenol molecule was accompanied by a change in toxicity, this change being different with each of the three positions of the group. In the case of the meta position there was a slight decrease, in the others an increase, p-cresol being the most toxic. Although the replacement of the oxygen of the phenolic nucleus with sulfur increased toxicity in the case of the cresols as well as phenol, the relative positions of the isomers were quantitatively the same in each class of compounds, despite apparent differences in the types of toxic action. The introduction of the nitro group resulted in compounds having a different quantitative relationship, although the para isomer was still the most toxic, as well as showing a markedly different relationship between the two variables concentration and survival time.

This paper presents the first of several studies of the toxicity of halogenated phenols, in which the same methods were used. As before, the goldfish *Carassius auratus* was used as the test animal, and for comparative purposes tests were also made with rotenone and phenol.

The three isomeric monochlorophenols, which were obtained from the Eastman Kodak Company, were subjected to distillation under high vacuum, and the constant-boiling fraction of each compound was allowed to crystallize in an ice-salt bath. The crystalline portion of each was then distilled at atmospheric pressure. For o-chlorophenol the fraction distilling at 175-6 degrees was used, for m-chlorophenol the fraction distilling at 211-2 degrees and melting

at 32 degrees, and for p-chlorophenol the fraction distilling at 216-7 degrees and melting at 38 degrees. All melting and boiling points are uncorrected. The samples of rotenone and phenol were from the standard stock previously used.

Experimental Procedure

The method of studying the toxic action of the substances was essentially the same as that previously described (5). Goldfishes of a single lot and weighing between 2 and 4 g. each were used, and a constant temperature of 27.0 degrees ± 0.2 degrees was maintained Determinations were made of the survival time in a series of concentrations of each compound.

Because of the slight solubility of the chlorophenols in water, acetone was used as the solvent in the preparation of stock solutions of the substances. From these the proper aliquot portions were taken to prepare the test solutions. In the latter a concentration of acetone higher than 1.5 cc. per liter was avoided. To assist in quick solution at some of the higher concentrations of the test substances where there was a tendency to partial separation, acetone was added to make this limiting concentration. All the substances formed clear test solutions at the concentrations required.

As in previous studies, the stock solutions of rotenone were prepared with acetone and those of phenol with water.

Experimental Results

The determinations are assembled in Table 1. A graphical comparison of the toxic action of the phenolic substances as expressed by these data is afforded by the survival-time and velocity-of-fatality curves in Figures 1 and 2. As in previous studies on phenolic compounds, the geometric rather than the arithmetic mean survival time was selected as the form of average defining best the position of each distribution and was used in the drawing of the graphs. Where desired in locating portions of the velocity-of-fatality curves, intermediate points were obtained from interpolated points on the survival-time curves. The indefiniteness of the curves just beyond the thresholds is indicated by dotted lines. The curves for rotenone are not shown, because they require a much more expanded scale.

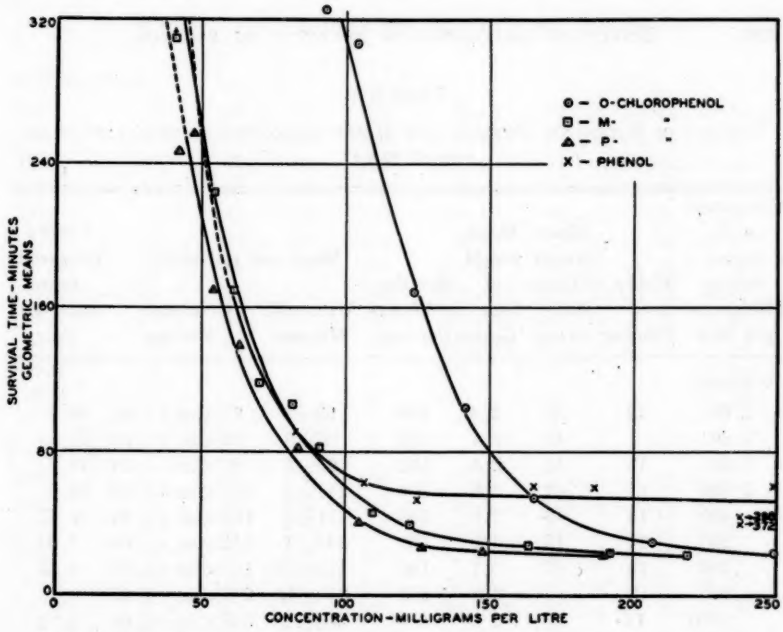

FIGURE 1 - SURVIVAL-TIME CURVES

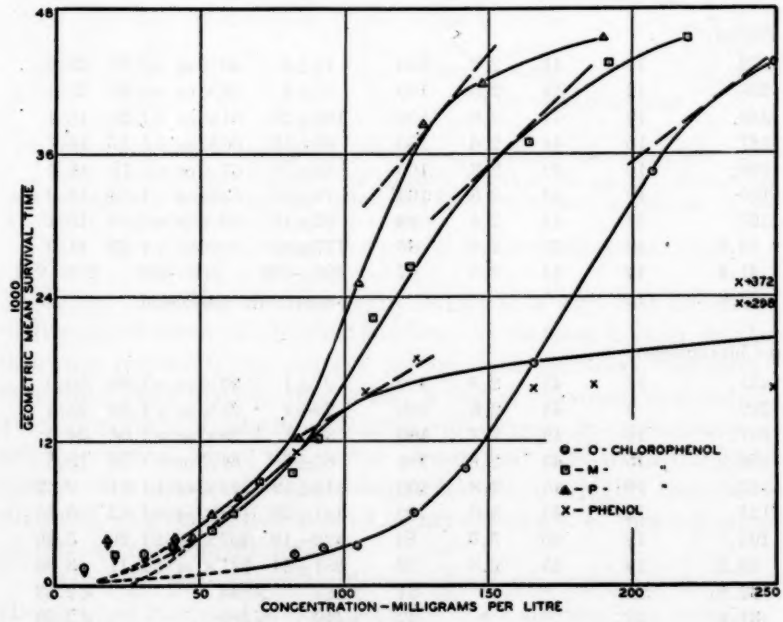

FIGURE 2 - VELOCITY OF FATALITY CURVES

TABLE 1

TOXICITY OF ROTENONE, PHENOL, AND MONOCHLOROPHENOLS TO GOLDFISH AT 27.0° ± 0.2°

Compound and concentration Milligrams per liter	Fishes used Number	Mean length of fishes Millimeters	Mean weight of fishes [1] Grams	Mortality in 8 hours Per cent.	Mean survival time [2] Arithmetic Minutes	Mean survival time [2] Geometric Minutes	1.000÷ Geometric mean survivial time
Rotenone							
2.00	12	45	2.8	100	93±3	92× or ÷1.04	10.9
1.60	11	43	2.5	100	86±3	85× or ÷1.03	11.8
1.00	13	43	2.5	100	90±3	89× or ÷1.04	11.2
0.600	17	44	2.6	100	101±3	100× or ÷1.03	10.0
.400	15	46	3.0	100	111±4	109× or ÷1.04	9.17
.200	14	46	3.0	100	143±4	142× or ÷1.03	7.04
.140	15	47	3.1	100	171±13	158× or ÷1.08	6.33
.100	13	46	3.0	100	250±16	235× or ÷1.07	4.26
.0600	14	45	2.8	86	354±18	343× or ÷1.05	2.92
.0400	14	[3]	[3]	50	>500	>500	<2.00
.0200	13	[3]	[3]	18	. . . .	. . . . .	. . .
Phenol							
372.	12	41	2.2	100	43±3	40× or ÷1.08	25.0
298.	12	43	2.5	100	47±4	43× or ÷1.09	23.3
249.	10	44	2.6	100	103±28	61× or ÷1.22	16.4
187.	10	44	2.6	100	90±21	60× or ÷1.17	16.7
166.	10	42	2.3	100	85±18	61× or ÷1.12	16.4
125.	10	43	2.5	100	79±18	53× or ÷1.14	18.9
107.	14	44	2.6	93	95±19	62× or ÷1.13	16.1
83.2	14	45	2.8	86	177±43	91× or ÷1.25	11.0
41.6	12	43	2.5	67	400—550	360—500	2.0—2.8
25.0	12	[3]	[3]		apparently unaffected		
o-Chlorophenol							
311.	11	45	2.8	100	21±1	20× or ÷1.03	50.0
249.	9	45	2.8	100	23±1	23× or ÷1.04	43.5
207.	10	48	3.3	100	30±1	29× or ÷1.04	34.5
166.	15	45	2.8	100	62±5	54× or ÷1.09	18.5
142.	10	45	2.8	100	113±12	104× or ÷1.11	9.62
124.	12	46	3.0	92	181±20	168× or ÷1.12	5.95
104.	12	46	3.0	83	336±19	307× or ÷1.10	3.26
93.2	19	45	2.8	79	381±24	327× or ÷1.11	3.06
82.8	11	[3]	[3]	64	>485	>395	<2.53
31.1	12	[3]	[3]	42	>440	>380	<2.63
10.0	10	[3]	[3]	20	>700	>700	<1.43

m-Chlorophenol							
219.	8	48	3.3	100	22±1	22× or ÷1.04	45.5
192.	10	44	2.6	100	24±1	23× or ÷1.04	43.5
164.	12	46	3.0	100	27±1	27× or ÷1.02	37.0
123.	10	48	3.3	100	39±1	39× or ÷1.02	25.6
110.	14	45	2.8	100	45±1	45× or ÷1.01	22.2
91.4	12	45	2.8	100	85±4	82× or ÷1.05	12.2
82.2	23	45	2.8	100	110±5	106× or ÷1.05	9.43
70.5	15	47	3.1	100	135±13	118× or ÷1.09	8.47
61.7	14	50	3.7	93	206±26	169× or ÷1.13	5.92
54.8	18	46	3.0	94	240±14	224× or ÷1.06	4.46
41.1	18	[3]	[3]	78	>335	>310	<3.23
20.6	13	[3]	[3]	62	>420	>390	<2.56
p-Chlorophenol							
190.	10	44	2.6	100	23±1	22× or ÷1.07	45.5
148.	12	44	2.6	100	24±1	24× or ÷1.02	41.7
127.	11	45	2.8	100	26±1	26× or ÷1.02	38.5
105.	12	46	3.0	100	41±1	40× or ÷1.03	25.0
84.4	11	46	3.0	100	87±6	82× or ÷1.07	12.2
63.3	12	47	3.1	100	152±13	139× or ÷1.10	7.19
54.3	14	46	3 0	100	181±12	169× or ÷1.07	5.92
47.5	13	46	3.0	85	289±29	257× or ÷1.12	3.89
42.2	14	48	3.3	86	302±31	247× or ÷1.12	4.05
18.1	10	45	2.8	90	>290	>265	<3.77
12.7	12	[3]	[3]	75	>330	>270	<3.70
6.3	13	[3]	[3]	54	>420	>320	<3.13
5.1	12	[3]	[3]	0	Very slight toxic effect		

[1] Estimated from length, which measurement excludes the caudal fin.

[2] The limits of error indicated are probable errors of the means. In the case of the arithmetic means they are differences from the means; in the case of the geometric means they are ratios to the means.

[3] The fishes were not measured but were of the same approximate size.

From inspection of the velocity curves it is seen that the effect of the introduction of chlorine has been to increase toxicity in the following respects: The isomers become toxic at lower concentrations than does phenol; they attain a higher maximal acceleration (rate of increase of velocity of fatality with increase in concentration), although phenol enters this region sooner than does the ortho compound; they maintain their maximal acceleration to higher concentrations and, as a result, they reach a higher velocity, i. e., they kill more quickly, at high concentrations.

Although the chlorophenols are about five times as toxic as phenol when compared at the thresholds, the concentrations necessary

to kill regardless of time, they are only about twice as toxic at the region of practically constant velocity, the minimal time of kill regardless of concentration.

Thus, the introduction of the chlorine atom, like that of the nitro group (4), results in compounds having a markedly different mode of toxic action from that of phenol. Toxicity is affected with respect to both concentration and survival time. However, the change of position of the atom, unlike that of the nitro group but like that of the methyl group (1), is accompanied by a change in toxicity very nearly, if not entirely, with respect to concentration alone.

Quantitative Comparison of Toxicity

A measure of relative toxicity found serviceable in previous studies is the minimal product of concentration and survival time (6). This measure ignores the two difficultly determined tolerance parameters and considers toxicity only in the range of most efficient action with respect to the two variables. Its value may be calculated directly from the survival-time curve or determined geometrically from the velocity-of-fatality curve by drawing the maximal tangent to the curve from the origin, as indicated by the broken lines in Figure 2. In the latter case the slope of this line, expressed in the units of the coordinates, will give the reciprocal of the minimal product.

The data for comparison by this criterion are given in Table 2. The minimal product of concentration and survival time is designated by $c_m t_m$, and, since toxicity varies inversely with this value, its reciprocal is also given. Its approximate coordinates, c_m and t_m, are given so that the region fulfilling this condition may be located readily in the graphs.

TABLE 2

RELATIVE TOXICITY OF ROTENONE, PHENOL, AND THE CHLOROPHENOLS

Compounds	c_m Milligrams per liter	t_m Minutes	$c_m t_m$ Gram-minutes per liter	Toxicity $\frac{1}{c_m t_m}$ Liters per gram per minute	Relative toxicity according to $c_m t_m$
Rotenone	0.100	215	0.0215	46.5	1.00
Phenol	104	63	6.55	0.153	0.00329
o-Chlorophenol	227	25	5.68	0.176	0.00378
m-Chlorophenol	160	27	4.32	0.231	0.00497
p-Chlorophenol	133	26	3.46	0.289	0.00622

From these data the relative toxicity of the isomers as compared with phenol is found to be as follows: ortho, 1.15; meta, 1.51; and para, 1.89. That this criterion gives a fair estimate of relative toxicity for compounds having such disproportionate parameters as phenol and a chlorophenol is indicated by the fact that, despite the relatively high resistance of this lot of fish which was especially noticeable against phenol, the ratio for the two compounds studied where this disproportion is most exaggerated, namely, rotenone and phenol, still is credible when compared with the results of three previous studies using different lots of goldfish not greatly different in age (1, 2, 4).

It is to be noted that for the isomers t_m is practically the same, and that therefore the comparison is a comparison of c_m. The ratios of $\frac{I}{c_m}$ are ortho, 1.00; meta, 1.42; and para, 1.71, as compared with 1.00, 1.31 and 1.64 for the measure $\frac{I}{c_m t_m}$. This again is a reflection of the fact that among these compounds the difference in toxicity is essentially an effect of concentration alone.

Results of Investigators on Other Test Organisms

Investigators of the bactericidal action of these isomers have reported various results (7, 8, 9, 10), but they all found the ortho compound to be the least effective.

Karpow (7) found the para compound to be more toxic to rabbits than the ortho compound when administered by subcutaneous injection. Binet (11), using emulsions, however, found little difference between the toxicity of the ortho and para compounds but reported the ortho compound slightly more toxic by subcutaneous injection to rats, just as toxic to guinea pigs, and a little less toxic to frogs. Kuroda (9), using 1 per cent. aqueous solution, reported minimal lethal doses by injection in the lymph sac of frogs and by intravenous injection in rabbits that showed the relative toxicity by that method of comparison to be—in the order ortho, meta and para—for frogs 1.0, 1.6 and 2.7, and for rabbits 1.0, 1.8 and 1.8.

Summary

A study was made of the toxicity of the three monochlorophenols with respect to concentration and survival time at 27 degrees, and

the results were compared with each other and with those for phenol and rotenone. Goldfish of the same lot, weighing between 2 and 4 g. each, were used as the test animals.

The introduction of the chlorine atom into the phenol molecule, like that of the nitro group, results in compounds having a markedly different mode of toxic action from that of phenol. Toxicity is affected with respect to both concentration and survival time. However, the change of position of the atom, unlike that of the nitro group but like that of the methyl group, is accompanied by a change in toxicity very nearly, if not entirely, with respect to concentration alone.

According to the minimal product of the concentration and survival time, which measures toxicity in its range of most powerful action, the relative toxicity of the chlorophenols as compared with phenol is as follows: ortho, 1.15; meta, 1.51; and para, 1.89.

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THE STORY OF ALLANTOIN

By Frederick R. Greenbaum, D. Sc.*

IN the middle ages we find in the British Pharmacopœia a description of Symphytum officinale, the comfrey root. Comfrey belongs to the Boraginaceae or Borage wort.

Comfrey root infusion was considered as an excellent healing agent. The infusion was placed on ulcers or was taken internally for stomach ulcers and amazing results were claimed.

By the end of the eighteenth century comfrey seemed to have declined in popularity among physicians. Before the eighteenth century comfrey was held in high repute by the medical profession. But even in the eighteenth century and later in country districts it was still valued by agricultural and other workers on account of its curative properties.

In later years it was spoken of as an "old woman's remedy."

It was not until 1912 that Macalister in England (1) became interested in wound healing and used comfrey infusions for wound healing. He submitted some of the ground and unground rhizome of comfrey to Dr. Titherley (2) who was then head of the Organic Chemistry Department of the University of Liverpool.

He found that the chemical analysis of comfrey root yielded the following substances:

1. Gums.
2. Sugars, including a reducing sugar.
3. Resins.
4. A protocatechuic derivative or derivatives.
5. A substance giving an intense yellow solution with sodium-hydroxide.
6. A crystalline solid, which was isolated in a pure condition. It was found that the root contained 0.8 per cent. of this crystalline substance. By accurate determination of its carbon, hydrogen and nitrogen contents showed that it possessed the same empirical formula as allantoin which greatly resembled it in its chemical properties.

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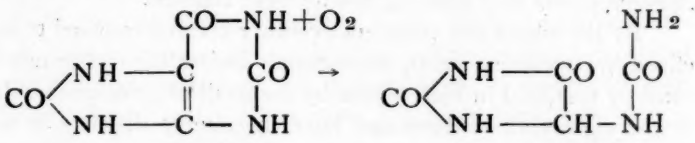
Chemistry of Allantoin

By comparison of the synthetic allantoin made from uric acid with the allantoin from comfrey root proved to be an identical substance by chemical methods. For example, allantoic acid and other derivatives were prepared from the chemically made allantoin and from that obtained from the root their melting points were the same and so forth.

Allantoin is a compound which is obtained by the alkaline oxidation of uric acid in the cold:



Uric Acid Allantoin

It is a white crystalline substance, melting at about 226 degrees C. with decomposition. It is only slightly soluble in cold water (0.6 per cent.) but readily in hot water. It is rather more soluble in cold alcohol but it is quite insoluble in ether. Dry allantoin is quite stable but if boiled with water for a considerable time it undoubtedly undergoes decomposition to some extent. It is decomposed by alkali, giving a variety of products, the nature of which entirely depends upon the conditions under which the experiment is carried out.

The Chemical Physiology of Allantoin

Allantoin is a product of purine metabolism. It is present both in animals and in plants. It received its name from the fact that it was found in the foetal allantoic fluid. Later on it was identified in the urine of pregnant women. Its presence has been demonstrated in very small amounts as a normal constituent of the urine of healthy people.

Numerous investigators, such as Schittenhelm (3), Wiechowski (4) and others have shown that when allantoin is given to man, it can be recovered to a considerable extent in the urine.

In the dog, cat and rabbit allantoin appears to be a normal end product of metabolism. Not so, however, in the human being. Human beings on a milk and vegetable diet excrete allantoin in very

minute amounts. This may be directly derived from the allantoin contained in the food.

It is interesting in this respect to note that this information was available as early as 1912 together with the clinical reports published by Macalister, but allantoin was not yet used in medicine.

Discovery of Allantoin in the Excretion of Maggots

It was not until 1935, when Robinson (5) discovered that one of the active principles of the excretion of maggots is allantoin Before this time, Malgaigne (6), W. W. Keen and Zacharias (7), and later on Baer (8) introduced the maggot therapy in medicine, particularly in the treatment of chronic osteomyelitis. Since the introduction of this treatment it has been employed in many clinics. The characteristics of treatment are rapidity of healing and increase of healthy granulation of tissue. Buchman and Blair (9) and Buchman (10) reported particularly on the effective way in which maggots remove necrotic tissue and reduce wound infection. Myers and Czana (11) and Robinson and Norwood (12) also reported how maggots aid in the healing process. J. C. Weil and his coworkers (13) reported success with this method. The unusual progress of healing, however, sometimes even in stubborn cases of long standing, has indicated that in addition, maggots secrete into the wound a substance which directly stimulates the healing process. This theory is expressed frequently in the literature (14).

Livingston and Prince (15) obtained the active principle by grinding live maggots in sterile saline solution and filtering the product through coarse and fine Berkefeld filters. Ferguson and McLaughlin (16) reported favorable results with maggot therapy.

But a decided step forward was only made when William Robinson (5) of the U. S. Department of Agriculture Bureau of Entomology published the results of his investigation and demonstrated the active ingredient of the secretion of maggots to be allantoin, a constituent of the urinary secretion of surgical maggots.

There are obvious disadvantages, however, in the maggot treatment of wounds. These are the difficulty in readily securing sterile maggots for application, the possible hazard of introducing additional infection into the wound from non-sterile maggots, frequent revulsion of the patients to this form of therapy, not infrequent extreme discomfort felt by the patient, due to the activity of the maggots in the wound and the high cost of maggots suitable for this purpose.

This discovery of Robinson, that allantoin is an active principle of the excretion of maggots, certainly brought the forgotten allantoin again to the attention of the medical profession. It brought wound healing from an empirical basis to a more scientific basis and American physicians were keen enough to avail themselves of this important and efficient drug—Allantoin.

Clinical Reports

The first paper which appeared after Robinson's discovery was that of Bethune (17). He noticed that allantoin seems *in vitro* to reduce the coagulation time of the blood. He gave 10 grams of crystalline allantoin to a patient on an empty stomach and injected intravenously 10 cc. of 0.5 per cent. aqueous solution of allantoin and no change in the coagulation time was noticed.

Bethune also in his paper used allantoin solution to irrigate the tuberculous and non-tuberculous lesions of the lung and pleura with definite healing and closing of the empyema.

The writer of this article (18) published a paper on "Allantoin, a New Granulation Tissue Stimulating Substance with especial emphasis on Allantoin in Ointment Form." The writer had developed an ointment containing 2 per cent. allantoin in colloidal dispersion, produced by a patented process (19).

In this paper five clinical cases are described which have readily responded to the treatment with allantoin solution, but particularly to the treatment with allantoin ointment. A case of a severe injury, one of a tuberculous ulcer, a case of severe third degree burn, and one of tuberculosis of the leg; and a case of amputation of a leg and a diabetic gangrene. All these cases were only treated with allantoin solution and mainly with allantoin ointment. Results were indeed very satisfactory as all of the cases healed completely and were able to return to work.

Kaplan (20) studied the allantoin treatment of ulcers. He offered the following conclusions:

"1. Allantoin, found in excretions of maggots and common to plants, can be prepared commercially.

2. It is stable and non-toxic.

3. It induces healing by stimulating healthy granulations and removing necrotic material.

4. Treatment is painless, simple and inexpensive.

5. It acts locally as long as allantoin is in contact with the wound.
6. Patients are ambulatory under this treatment.
7. Overgrowth of granulation tissue can be checked by discontinuing applications.
8. Allantoin seems to have the curative effect on chronic ulcers as the introduction of maggots and it is less troublesome for the physician to administer and less disturbing to the patient than the use of insects."

Allantoin also has a definite field of usefulness in the field of dentistry. Gordon (21) in a paper entitled "Use of Allantoin in the Treatment of Osteomyelitis of the Mandible" cites a case of osteomyelitis of the mandible treated with hourly irrigations with allantoin. Healing set in and the entire treatment was ambulatory and proved entirely beneficial to the patient.

Sussman (22) reported on the use of allantoin in osteomyelitis of the mandible, fracture of jaw, etc. He arrived at the following conclusions: "It seems to us that in allantoin we have another drug, which can be added to our armamentarium for the treatment of suppurative conditions. It appears to stimulate the formation of granulation tissue and reduce the time element in the healing of these conditions."

Comunale (23) reported on the use of chemically pure synthetic allantoin in the treatment of osteomyelitis. He reported the following results:

"1. When allantoin is used as a 0.4 per cent. solution, the drainage is copious, thin, yellow, without odor.
2. The drainage resembles that which occurs when maggots are used.
3. The edges of the healing wound are similar to that occurring with maggot therapy.
4. A quicker, natural debridement seems to occur when allantoin is applied as an unguentum into the cavity."

Comunale made the following comparison between maggot and allantoin therapy. (a) A fine meshed cage must be prepared for the maggots. (b) They must be implanted twenty-four to forty-eight hours after being obtained from the laboratory. (c) They are repul-

sive to both the physician and patient. (d) They need wide incision of wound and must have either natural or artificial light. (e) Must be washed out at the end of five or six days with saline, as they reach maturity and die in their own excretions. (f) No antiseptics can be applied when implanting maggots.

Allantoin (a) can be obtained chemically pure, free of objectionable substances and of tetanus organisms; (b) can be used in hematogenous, acute or osteomyelitis as a wet dressing, instillation or ointment pack; (c) allantoin is the active principle which maggots excrete and can be placed in the wound for longer intervals.

Robinson (24) in a report of the Smithsonian Institution stated that in the four years that this drug was in use so far no harmful effect was obtained.

Allantoin used to be a laboratory scarcity but according to Robinson in 1937, about 300,000 grams of synthetic allantoin crystals are now being produced annually. This amount would make 140,000 pints of the 0.4 per cent solution, or over 500,000 ounces of 2 per cent. allantoin ointment.

He also states "it remains to be seen, whether the popularity of allantoin will continue or whether it will suffer the fate of many other new drugs and eventually fall into disuse. At any rate, the present response to its discovery in maggot secretions is in strong contrast to the reception given to previous discovery by Macalister in the roots of comfrey."

Since this report was published Allantoin's popularity has still increased. Various clinical investigations are under way with results to be published soon.

Experiments With Plants

As allantoin has definite cell stimulating effect and also an effect upon the formation of tissue granulations, it was obvious that allantoin may have a growth stimulating effect upon plants.

If bulbs of hyacinths are placed in solutions of allantoin, varying in strength from 0.1 to 0.5 per cent. it was found that the growth of the root was inhibited in a ratio proportionate to the amount of allantoin in the solution, that is, the stronger the solution, the less was the amount of growth in the root. It appeared, therefore, that allantoin did not promote cell growth when added to the water in which the bulbs were growing, in fact their growth appeared to be retarded.

Then the effect of injecting a solution of allantoin into the bulbs was studied and a number of experiments were conducted along these lines. The allantoin injected into the bulbs of hyacinths, tulips, chrysanthemums, acted as a cell proliferant, forcing the growth of the shoots and especially of the flowers.

From the experiments one gains the impression that allantoin is a substance which is capable of being utilized by vegetable cells in connection with their proliferative properties in connection with certain animal cells. In both cases the reproduced cells are normal microscopically and resemble those from which they took their origin.

Allantoin and Leucocytosis

Macalister has observed that the oral administrtaion of one grain of allantoin in solution, given by mouth at two hour intervals, on an empty stomach, will increase the polynuclear cells by from 5 to 15 per cent. and it was noted by subsequent counts that they had returned to the normal in from sixteen to forty-eight hours.

Dr. M. Schwartzman (25) (Macalister's book, p. 48) administered some freshly prepared allantoin to nineteen people and he obtained in seventeen cases positive results up to 65 per cent. increase in the number of leucocytes.

Following this idea of Macalister, we (26) investigated on rabbits and dogs the leucocytic effects of allantoin after the intravenous and intramuscular injections as well as after the oral administration of allantoin. The detailed results of this investigation have been reported elsewhere. Suffice it to say, that we have been able to confirm the findings of Macalister and Schwartz, and allantoin, immaterial as to the route of administration, definitely increases the leucocytes, particularly the neutrophiles. Clinical investigation, to study the effect of allantoin on the number of white blood cells, are at present under way. As allantoin is a bland, inert, non-toxic substance, the fact that the oral administration of allantoin, which is entirely harmless, should increase the polynuclear cells, particularly the neutrophiles would be of great value in cases of low grade infection, mostly of a chronic nature of obscure origin. By the administration of allantoin, the white blood cells would be increased and thus the infection would be overcome by the antagonistic action of those increased white blood cells.

Metabolism of Allantoin

We attempted to find out what happens to allantoin first, when it is injected intravenously into the blood stream, second, after it is ingested orally to rabbits.

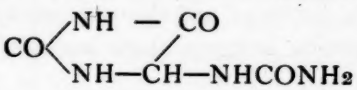
After the intravenous administration of allantoin into rabbits (10 cc. of 0.4 per cent. solution was injected) it was found that within three-quarters of an hour after the injection, the maximum concentration of allantoin in the blood was reached (38.5 mg. of allantoin) and after about three to four hours, all of the allantoin was thrown out of the circulation and the blood contained only the normal concentration of allantoin, about 5 mg. This shows that allantoin in concentrations greater than 5 milligrams is a substance foreign to the blood and is very rapidly eliminated from circulation.

As to the second question regarding the fate of the allantoin after the oral administration of allantoin to rabbits, it was found that Larson's method (27) for the colorimetric determination of allantoin, due to the interference of creatine, gave too high values. A new and direct method for the determination of creatine was then developed by Schaffer (28). He also showed that allantoin injection causes excretion of large amounts of creatine. Schaffer and Greenbaum (29) developed a new method which eliminates the creatine interference. This was done by precipitating the allantoin as the mercuric allantoinate. It was also found that allantoin ingested by rabbits is completely absorbed and subsequently excreted by the kidneys. No allantoin could be detected in the intestinal excreta.

Allantoin recovery experiments after ingestion of tared amounts by rabbits, indicate quite an excess over that ingested and normally present. This excess was traced partially at least to the liver. This organ loses its normal concentration of allantoin when that substance is fed. It was also found that if allantoin were fed to rabbits in amounts above 250 milligrams per kilo of body weight, a decided loss in weight occurred. This would seem to indicate that the excess creatine was derived from cellular creatine.

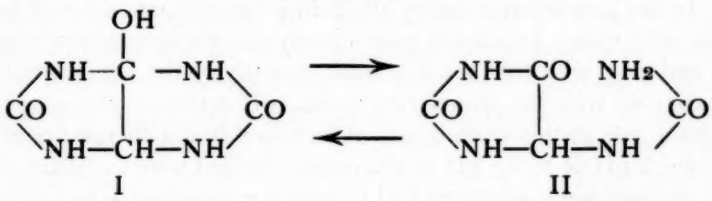
The Chemical Constitution of Allantoin

Titherly (30) showed that Grimaux original formula



will not explain all its properties, especially the optical inactivity. Its molecule on Grimaux' formula contains an asymmetric carbon atom, namely, that in the CH grouping and like other compounds containing an asymmetric carbon atom, allantoin should be optically active.

Titherley, in order to explain the apparent abnormality of allantoin, supposed it to be a tautomeric substance in which a double ring formula (I) alternated reversibly with that of Grimaux (II).



I II

This alternation between I and II is promoted by the shift in position of one of the hydrogen atoms believed to be mobile.

Formula I is strictly symmetrical, therefore, optically inactive, but when it shifts back to formula II containing an asymmetric carbon atom, it must yield an equal number of molecules of dextro rotatory and levo rotatory allantoin, and the d. l. mixture must be optically inactive by compensation.

This theory of tautomerism has received confirmation by the researches in France of Fosse, Thomas and Graeve (31) (p. 52 Macalister). They have shown that it is actually possible to prepare optically active forms of allantoin if great care is exercised to prevent what is called racemization. This means that an initial dextrorotatory compound steadily loses its activity and ends by being completely inactive like water.

Allantoin as it is ordinarily obtained is such a racemic compound of the two forms and if one of the two forms is isolated, it passes with extreme ease into the racemic form, as it would be expected to do if there is an alternation between the two molecular formulæ I and II.

Natural allantoin when it is isolated from natural sources, by carefully controlled methods to prevent racemization, is optically active and is the d. allantoin. It has a specific rotation for polarized light $(d)_0^{22}+93°$ in water and this hitherto unknown form of allantoin has been obtained from calves' urine and from certain plants, by extraction method avoiding all rise of temperature.

L. allantoin has been obtained by an enzyme from soya bean, called allantoinase, the l. form surviving as the d. allantoin ferments more rapidly. Both d. and l. allantoin are exactly alike, each on warming in solution passes over into the racemic form, common allantoin.

When, therefore, ordinary racemic d. l. allantoin is applied therapeutically it may be presumed that only one-half of it (d.) is active and the other half (l.) is inert, but as yet nothing definite is known about this. In any case when ordinary allantoin is brought into solution by heating with water, it no doubt passes partly into the symmetrical ring form and even with cold water a small quantity of the asymmetrical form coexists with the symmetrical form. pH seems to play a very important role in this connection. Allantoin solution should preferably have a pH of 7, the pH of the purest distilled water. Allantoin being an amphoteric substance and therefore very sensitive to acidity and alkalinity, as well as to high temperature, there is reason to believe (after the work of Fosse, Thomas and Graeve) that the predominating form in neutral solution (pH = 7) in the cold is the asymmetrical form II.

Urea

The close chemical relationship that exists between allantoin (glyoxyldiureide) and urea, made it obvious that urea also possesses some cell proliferating action. As a matter of fact, one year after the discovery of allantoin in the excretion of maggots Robinson (32) reported on the fact that urea is also a substance of excretion of the maggots and he advocated a 2 per cent. urea solution.

Holden and Mackay (33) used strong solution of urea and claimed that it dissolved protein and protein substances.

Baker (34) used 30 per cent. or higher concentrations of urea solution or urea crystals. Muldavin and Holtzman (35) used urea crystals.

In a rather recent paper, Holden and MacKay (36) used a 40 per cent. urea solution or even crystals of urea.

There is a tendency to dry out and cake on occasion and the difficulty of maintaining them in proper contact with the tissue at times.

Very frequently the use of concentrated urea solution is accompanied by pain. This pain is so pronounced that a local anesthetic has to be added to the concentrated urea solution.

If we compare allantoin as a healing agent with urea, we must admit its superiority, because even in a dilute solution of 0.4 per cent. the granulation which appears is healthy, pink and flat and superior

to that produced by any other healing agent. Allantoin never produces pain; there is no need for the addition of an anesthetic. Of course, in view of the fact that only a very dilute solution is used, no caking occurs and intimate contact is established whether the solution or the ointment is used.

Very recently Robinson (37) has found that in the excretions of maggots is contained, besides allantoin and urea, large quantities of ammonium bicarbonate. He demonstrated that a 1-2 per cent. solution of ammonium bicarbonate possesses marked healing properties.

It seems to me that urea and ammonium bicarbonate obtained from urea by the enzyme urease are decomposition or deterioration products of allantoin. While these decomposition products possess healing action, as has been demonstrated, is it not reasonable to assume that allantoin, which has healing action in such low concentration is far more powerful as a tissue granulating and stimulating agent?

We have under way at the present time, comparative, carefully controlled studies between allantoin and urea and we hope we shall be able to report the results of these studies in the near future.

We have presented the "Story of Allantoin" as a progress report, covering a period of five years of extensive use of allantoin. We feel today, just as we felt five years ago, that in allantoin we are dealing with a most remarkable drug of great promise and possibilities.

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RESEARCH AS A RACKET

By T. Swann Harding

THE human race has always been amply endowed with curiosity. It wants to know how and why. Regardless of sex it wants to know. Men are just as curious as women. Perhaps they are even more so because it was apparently men who first made a life vocation of curiosity.

For the early alchemists, mystics, and astrologers were simply men filled with curiosity who wanted to know how and why things happened as they did in the world about them. Ultimately this sort of curiosity was organized upon certain theoretical principles. The hypothesis replaced the guess. Science appeared. Research followed.

For what we so respectfully call reasearch is nothing but the organized curiosity of intellectually endowed and scientifically trained individuals seeking to discover how and why things happen. Research was originally the refined pursuit of wealthy amateurs who could finance their own excursions in idle curiosity.

Possibly because they stood the expense they considered it their right to be secretive. They imparted little knowledge. Hence scientific information accumulated very slowly at first. But very gradually research ceased to be a calling and became simply another of the professions.

It had been found that many things which scientists discovered at research could be exploited commercially. Colleges and universities began to train future research workers, topping the training off with a three-year period during which the student himself performed minor researches as a rehearsal for his future career. Still the profession was dignified.

But the educational doctrine got abroad, and was much propagated by educators who should have known better, that the longer you went to school or college the more you were likely to earn later. This was a very pernicious doctrine, destructive of education's finest characteristics.

As a result research, like medicine, pharmacy, and the law, became a mere occupation for which one trained vocationally and at which one worked on salary. So many were imbued with the idea that higher education was a mere preliminary to higher earning capacity that research finally became in large part a racket.

Research can be a racket in two ways. The knowledge discovered by legitimate scientists can be exploited commercially in wrong ways, or individuals vocationally trained in science can be set to doing a sort of pseudoresearch in order to bolster a fraud on the public. That is making research willingly or unwillingly an adjunct to commercial racketeering.

But research may also become a racket much more subtly. Just because our annual production of doctors of philosophy, presumably able to perform research, exceeds our legitimate requirement, it is difficult to find something to occupy them. Many of them go into research and work on projects they are really unable to advance. Many of them work on silly and rather absurd projects and publish worthless papers.

The futility of much research is frequently remarked by those in a position to judge. Thus in the *British Medical Journal* for January 9, 1937 you will find Dr. Robert Hutchinson of London writing that the first impression derived from any survey of medical science today is one of confusion. An immense amount of ill-conceived and ill-directed investigation into the causes and treatment of disease is going on.

As a result "much socalled 'research' is a mere beating of the air, a form of solemn trifling, wasteful alike of time and money. This confusion is reflected in medical publications, which have become excessive in number, and often so highly specialized that their very terminology is only to be understood by the initiated; full of facts and observations, but poor in ideas, in fertile hypotheses, and in helpful generalizations."

It is a fact that in spite of all that goes under the name of medical research the killer diseases—pneumonia, cancer, nephritis, organic affections of the nervous systems, influenza, rheumatism, and the common cold—slay on, little understood. We have cyclopedic knowledge about cancer, to be sure, but we know no curative method for it.

This at first seems strange. A possible explanation is that research workers quite naturally prefer to work upon something that will enable them quickly to write and publiish a paper. The big problems are not only difficult and time-consuming, but they do not readily lend themselves to paper production. And, as Hans Zinsser said in *Science* for October 23, 1931:

"We have developed the habit of judging men for positions by the perusal of the titles of their publications, and a list three pages long is more formidable than one of a few lines." This places a premium upon "the mere activity of investigative effort regardless of its intelligence or results . . . a hot-house forcing of medical (and other) investigation which, together with some very brilliant and useful growth, has nourished the weeds of second-rate material."

Medical and scientific "discoveries" readily lend themselves to press exploitation. We live in an age of cheaply vulgarized sensations. Institutional rivalry, each institution bidding for support, leads to premature submission of results to the public in the effort to evoke popular applause. A curious halo also surrounds research even in the absence of talent. Yet, as Zinsser noted, there probably are more useful and less expensive methods of occupying time if one is ill-trained or not gifted.

In his book *The Scientist in Action* the British physicist, W. H. George, mentioned "pump-handle, safety-first or pot-boiling" research which rapidly turns certain scientific workers into "paper merchants or paper machines."

For instance a gifted man like F. Gowland Hopkins makes a fundamental observation that adding milk to a supposedly complete basic diet will prevent rats from dying. That observation opens up a thousand little problems for little minds; all sorts of diets and animals can be tried. The same would be true of a discovery that thyroid gland substance if fed to rats affects the size and composition of their bones.

The pump-handlers can then try rats of both sexes, at all ages, on every conceivable kind of diet; they can then proceed to other glands and other animals. Again: if some now physical constant of a chemical element is found, there are ninety-odd such elements. There are a quarter of a million chemical compounds available. Determinations can be made on each. Papers abound.

> "Given the requisite technical skill, the greater the industry in this kind of research, the more the established results (facts) just as, under normal conditions, the water flows so long as the pump handle is worked. There are no risks of getting results difficult to interpret, or difficult to present in a scientific journal, for which reason a scientist who publishes much of this kind of research is called a 'paper-merchant' or a 'paper-machine.' "

Naturally the very availability of funds for "research," which so many righ-minded laymen regard with mystic awe as close to the miraculous, promotes second-rate production and racketeering. Zinsser said in 1931 that available funds had then outstripped our ability to use them wisely in research.

Philanthropists had fondly hoped that money would engender ideas instead of being the mere fertilizer which may possibly aid the sprouting of the living seed of thought. Hence much work was undertaken then, and is now, "merely to justify expenditure." Hence many individuals sit in well-equipped laboratories upon lifeless ideas, "like a hen on a boiled egg," or else spend time and money "transposing into complicated notations old tunes that have been adequately played in C major."

A certain amount of this grubbing and gnawing of dry bones is inevitable. Pedantry has ever been attracted to the dustbin. Allowance must also be made for trial and error and the necessary repetition of important work. But it requires intelligence to discover that a line of research has led into a blind alley and that return to the highway of progress can be had only by retreat.

Grants for specific purposes often force research workers to attack the wrong problems, or the right problems at the wrong time. For it is sometimes impossible to solve one problem until certain other research has been done. Perhaps the necessary equipment or methods are lacking. Thus perfection of high-power centrifuges went far towards enabling scientists to penetrate the mystery of infective viruses.

Research projects are sometimes selected in curious ways. Various institutions vie to secure the problem and the grant. Later individuals within the institution jockey for position. If the grant is for a specific kind of research the workers must often continue hacking at a hopeless problem when other lines of research would be far more remunerative.

Since the usefulness of a research worker or institution is judged so largely by the quantity of publications issuing therefrom, there is a strong temptation for workers to attack little fractions of problems that lead to quick publication. There are also fashions and fads in research and each institution feels it must do a little of this or that because others have won the limelight at such work.

Meanwhile the march of the doctors from institutions of higher learning continues relentlessly. Prof. Luther P. Eisenhart of Prince-

ton remarked this in *Science* for February 14, 1936. Whereas the degree was originally intended to signify that the bearer was a scholar, had acquired particular mastery over his field of study, or has shown a capacity for independent research, this was no longer true.

The doctor had rarely enlarged or modified the field of human knowledge. He had rarely presented some significant interpretation of data. The degree was and is instead a badge indicating that three years additional work was performed after graduation as a bachelor. It is merely an advanced degree not a certification of scholarship. But it has become the passport to research or teaching and those who apply without it receive scant recognition.

Actually, as Prof. Eisenhart said, holders of the degree may be very deficient either as teachers or as reserach workers, but universities and research institutions are ranked in accord with the number of doctors of philosophy they employ. The Mathematical Association of America says, however, that most of those who get the degrees never carry on significant research.

But the doctors must be kept busy. Hence the startling output of learned nonsense. Hence, whereas *Chemical Abstracts* published brief summaries of only 7975 articles in the field of chemistry the year it was founded, 1907, it epitomized 42,468 in 1935, and should make the count 135,000 by 1985 if "progress" continues unabated.

But let us follow a doctor as he approaches the director of a research laboratory dedicated to work on sugar. He inquires about a position. The director begins by denouncing cane and beet sugar as bad for human beings because the body has to break such sugar down into the simpler sugars dextrose and levulose during digestion. Since the stomach acid easily accomplishes this it is difficult to see what harm occurs.

But the director says it is absolutely necessary to make these simpler sugars, and others, on large scale to save the health of the race. Now levulose might be especially good because, of course, diabetics could utilize it better than they can ordinary sugar. This is unproved; little evidence supports the idea—but it makes conversation and possibly research projects.

The director then told with enthusiasm how his institution had managed to produce one rare sugar at a dollar a pound which formerly cost $250 a pound. Of course no one would buy it anyway because it had no known use, but even then . . . Maybe it might have

dietetic uses in the future. How it could have when it was a five-carbon sugar and our organisms reject such sugars, no one could say.

Furthermore this institution had also produced a very, very rare sugar anhydride worth $50,000 a pound. It got a big write-up in the press too. The price was purely artificial, of course. This was a pure research project. The material was found lurking in dandelion stems and promptly some old lady wrote in wondering if she could lift the mortgage on her home by selling the institution dandelions!

Then there was honey, went on the director. Maybe we could find some vitamins or useful minerals in honey. We could do work on the special nutritive value of honey, or on its standardization, or on its medicinal value, or on means of preventing it from crystallizing, or on the possibility of using it in baked goods and confectionery. There were no end of things to do. Even honey economics might be studied.

It is easy to see how research can become a racket. There is the raging epidemic of iradiation with ultraviolet rays. This reached over into entomology and bees were irradiated. Some apiarists began to irradiate queen bees and to advertise them as improved egg layers as well as productive of broods of sweet-tempered, less irritable bees. Careful investigation disclosed that the rays had no beneficial effects on bees at all.

One careless pump-handle paper thus makes other investigation necessary. For someone must work to disprove the theses set up by those who rush to print so rapidly that their publications abound in factual errors and dubious hypotheses. Almost any scientific journal extant will disclose to the eye of the expert observations, statements, or entire research papers that not only did not merit publication but also confound other workers and tend to confuse the issue in various fields.

A scientist for instance attempts to show that certain breeds of chickens are more resistant than others to certain worms. But chickens of one breed give precisely opposite results on different trials. This he at once "explains" by stating there must be two different strains within the breed.

But the chickens also show a varying resistance at different ages. Finding himself cornered the scientist ultimately explains this by holding that the worms used were sometimes more vigorous than usual. Soon he had started to argue that each breed of chickens had within it

resistant and susceptible strains. Then he assumed that the few birds he used really represented a fair sample of all birds of their kind.

That is—except for the White Leghorns. They proved so susceptible that he decided they were the normal host for this worm and the other breeds were abnormal or resistant hosts. Actually all chickens apparently descend from one original species. We lack grounds to assume that present breeds are species, or that they represent more than transitory variations. Certainly we do not understand their genetic composition.

This investigator was really reporting the results he secured when he used fortuitously selected groups of individual genetic character, among which groups certain individuals varied. Environmental conditions would make another similar experiment almost certainly turn out differently. Little had been produced except a complex and reasonably impressive way of wasting time and money. Many other papers would analyze similarly.

In conclusion suppose we take a field of research and see what is being done therein, the cancer problem. In order to have expert guidance in our analysis, and avoid ignorant prejudices, let us follow the address Dr. James Ewing of Memorial Hospital made to the National Academy of Science on April 25, 1938. His title was: "The Public and the Cancer Problem."

Cancer is not, strictly speaking, a disease. It is a basic abnormality in growth that ramifies in many ways and produces a complex of diseases. Certain cells, usually in middle-aged or older people, just go on a growth rampage and multiply regardless of the needs or health of the rest of the bodily organism. Hence it is totally unscientific to seek a "cure" for cancer.

There is no known single cause of cancer, hence can be no cure, despite the many research projects directed towards finding one. Such malignant growth includes all classes of forces known in nature. The malignant growth process is obscure just as is the normal growth process. Growth itself is a complex thing implying progress towards maturity, increase in weight, multiplication of cells, and specialization of cell function, not to mention possible increase in cell size.

A disease that spreads so rapidly and so seriously over so many organs and structures of the body could scarcely be "cured" even if arrested. The body might be restored to a condition of impaired service and life might be prolonged. Yet persons of large means have re-

peatedly made the mistake of granting money for the direct discovery of the cause and cure of cancer.

Some make the mistake of listening to "fervid tales of pseudoscientific adventurers or outright imposters, who begin by decrying the methods of orthodox medicine, overemphasizing so-called medical intolerance. . . . The benefactor knows nothing about medicine and the pseudoscientist knows nothing about cancer, and both cordially deceive each other."

Dr. Ewing states: "Certain well-known projects of this class have grown to enormous proportions, involving the expenditure of millions of dollars, deceiving thousands of patients, surviving repeated public exposures, migrating from one unused territory to other virgin soils, but often gaining steadily in support from a small proportion of misguided souls in and out of medicine and reputable society."

The socially elect and wealthy layman tries to sustain the "persecuted" scientists and visualizes notoriety from discovery of a cure. Pseudoscientists often migrate mysteriously from one pasture to another. They land in the most prominent and oustanding laboratories from time to time and remain until exposed. Often they move to Europe and gain a foothold after being kicked out of reputable American laboratories—and vice versa. The gambling spirit dominates their financial supporters.

Another group of philanthropists desires merely to find a cure for cancer. It will give elaborate support to unattached physicians—honest, orthodox, but not expert in cancer. Benefactors usually have high intelligence but poor sagacity. Newspaper publicity attends the initiation of projects. Many pathetic patients are attracted. The publicity is repudiated by the sponsors. The methods used are loosely ethical and a certain amount of scientific talent is involved, but the publications tend to appear in the semi-medical or popular press.

The promoters and "researchers" do not dare sometimes to present their results to their peers. Yet the life of the project is often tenacious. It depends largely upon the isolation of the promoter and the patience and loyalty of the benefactor. Semi-scientific cancer cures arise with alarming frequency. All this pseudoscientific work diverts both attention and funds from the so much needed basic research in cancer.

Dr. Ewing declared: "Finally the determination to go after the cause and cure of cancer has been the impelling motive in the creation of some of the most important bequests now available in cancer

research, and the feeling that sensational discoveries were imminent dominates the activities of some of the highest official scientific organizations. Thus the worthy donor of one of the largest gifts hopes, by greatly increasing the number of workers, to hit by chance on the fortunate lead. Another donor urges the immediate investigation of the more appealing cancer cures announced in the newspapers."

Very often wise and sagacious research directors are replaced with charlatans who claim everything in sight. There is undignified resort to salesmanship. Much is said of martyred and persecuted genius. This system of research attracts inferior, incompetent, notoriety seekers. Much money is wasted. Many quacks are encouraged. But the useful research is basic in character and unlikely to yield any immediately beneficial or practical results in treating cancer.

Among such basic approaches are: Genetic studies; chemical studies of normal and abnormal growth and tissue metabolism; chemotherapy—the search for substances that will scotch the cancer and not injure the sufferer; studies in physical chemistry of osmosis and electrical cell structure; investigation of the theory of embryonic organizers; the approach of microbiology via parasites; the ultrafiltrable viruses; the so-called cancerigenic substances derived from coal tar; chemicals that control growth processes; X-rays and so on.

The steel industry is said to spend ten millions a year on research —a little less than the total capital invested in American cancer research. It is not true to say, of course, that large grants of funds and the employment of platoons of workers would solve the cancer problem in five years, as some have suggested. But small grants in aid for little, ill-equipped projects to be carried on for short periods are pernicious.

In the *Journal of Heredity* for July, 1938, Dr. F. S. Hammett called attention to the necessity for organization of research on a broad basis. This should be national in scope and should look ahead far. Isolated research institutes should not be multiplied further. Cancer research also must be robbed of the glamour it still has in the public mind.

What is so shockingly true of cancer research is quite typical of research in general. As at present organized—occult, esoteric, behind walls, research can readily become a racket. Its tendency to overproduce doctors of philosophy and publications tends to make this a self-perpetuating system.

As Hammett observed the kind of research institute founded perhaps by a single individual to work on a single project or idea is always bad. Soon the donor, the proponent of the idea, and even the problem itself will die, and we have a sort of fully equipped mausoleum, plentifully supplied with staff, apparatus, and supplies, yet a tomb.

Research even on a biological topic must be broadly based. It must have its experts in physics, in anatomy, in genetics, in chemistry and in the social sciences. Institutes should be established not so much on a basis of disciplines, as on that of the fundamental properties of nature—reproduction, growth, nutrition, and so on. Expressions of these processes would be integrated and correlated, the various scientific disciplines being used for the purpose as needed.

Order would be brought out of chaos. Coordination between several aspects of the problem would occur. The path would be opened for the integration of scientific findings into daily life. There would be a lessened flood of essentially unrelated scientific publications and papers. There would be a drop in the number of journals needed for the publication of scientific findings, and these are now so numerous as to swamp serious workers.

Research must be organized on some such broad, long-time basis. It must seek answers to the questions that arise and demand solution in our society, while at the same time giving free play to the spirit of pure inquiry. It must devise ways of molding our social and economic organization into more rational forms.

Research in any particular field—cancer, agriculture, steel, or what not—must be unified to the extent necessary to prevent duplication, suppress racketeering, dispense with unnecessary publications, and utilize funds to the best advantage. There must be more intelligent allocation of funds and less tendency to judge an institute or an individual by the poundage of publication produced.

The field for racketeering is unfortunately large in the United States. But it should include no part of the realm of science.

ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

The Use of Bulk Ether in Surgical Anesthesia. E. M. Hediger, M. B. Chenoweth and H. Gold. *J. A. M. A. 114,* 1424 (1940). Previous workers have stated not to be entirely true the belief that U. S. P. anesthetic ether deteriorates rapidly and is unfit for use 24 hours after opening of the container. Ether deteriorates on being exposed to heat, sunlight, air and certain catalytic agents. Gold, in 1934, showed that bulk ether does not show appreciable chemical change when stored in the usual anesthetic ether cans, opened frequently, stoppered tightly each time and kept at room temperature for a number of weeks.

Hediger and Gold, Dooley and associates, Morrison and Turner later reported that bulk U. S. P. ether could be satisfactorily transferred to cans, stoppered with cork, and used. The former workers observed 702 surgical anesthesias with one commercial brand of bulk ether placed in anesthetic ether cans, stoppered with corks. They found it to be chemically pure and clinically indistinguishable from fresh ether in small sealed containers.

Due to contradictions in the label statement of some commercial U. S. P. ether, the authors quantitatively investigated impurities, the speed of deterioration under various conditions, and a comparison of bulk ether transferred to cork-stoppered ether tins, with ether in small sealed metal containers.

The samples were tested for peroxides, aldehydes and acids. The effects of temperature, cork, access of air, repeated opening and cork stoppering, clear and amber bottles, daylight and bright sunlight were determined.

Sunlight was definitely unfavorable. Ether in amber bottles in bright sunlight deteriorated very slowly over a period of two weeks or more. In clear glass, definite impurities were revealed at the second day. Warm temperatures hastened formation of impurities, but not so rapidly in absence of light. Ether stored in clear glass in a dark closet was stable for a three week period. After 63

days of identical storage, ether in amber glass in a dark closet showed no impurities.

Bulk ether U. S. P. XI stored in a 27-lb. drum, opened and stoppered repeatedly, showed no impurities in 64 days.

Presence of ground cork in ether cans did not promote deterioration.

Access of air caused no significant deterioration but the ether evaporated in two weeks.

When stored in anesthetic ether cans, opened repeatedly and kept at room temperature or in refrigerator, ether showed no significant impurities.

Two thousand surgical anesthesias were observed clinically on more than 16 different types of operations with bulk ether and small can ether. Cases of vomiting during induction and maintenance and postoperative pulmonary complications were similar in distrbution wth the 2 types. Eighty-five and eight-tenths per cent. of 1,030 anesthesias employing bulk ether were satisfactory, and eighty-six and three-tenths per cent. of 835 anesthesias with ether from small cans were satisfactory.

Hediger and associates state in conclusion that hospitals may safely use bulk ether for anesthesia. A copper siphon arrangement or funnel may be used for transferring from a 25-lb. drum. This will be stable for a period of a month. In smaller institutions 5-lb. cans may be used to supply the small cans. M. O. H.

Vitamin A Destruction in Fish Liver Oils and Its Relation to Peroxide Formation. E. J. Simons, L. O. Buxton and H. B. Colman. *J. Ind. & Eng. Chem. 35,* 706 (1940). Considerable research has been conducted on the subject of the loss of vitamin A in fish liver oils. It has been established that peroxides developed in the oil by oxidative changes are responsible for this destruction. The authors have studied the changes in various fish liver oils and correlated the development of peroxide with loss of vitamin A.

Samples were stored at 34.5° C. and the peroxide level determined at various intervals iodometrically. The vitamin A level was determined on the spectrophotometer. It was found that the oils tested fell into two groups, group I consisting of cod, pollack and U. S. P. reference oils and group II of halibut, dogfish and sword-

fish liver oils. In group I the percentage of vitamin A oxidized at various peroxide values was smaller than in group II at similar peroxide values. This classification is not influenced by the individual resistance of the oils to oxidation as some of the most stable and unstable oils occur in the same group. Neither can the difference be explained on the basis of differences in original vitamin A concentration. When stored at room temperature the same division was observed although a higher peroxide value was required to destroy a given percentage of vitamin A than was the case in the oils stored at 34.5° C.

The division of the oils into groups is probably related to their composition. Although complete analyses are not available, the fatty acid composition of oils from some of these species was reported by Schönfeld. The fatty acids of oils of group I consists of a high percentage of acids with more than one double bond. The oils in group II contain fatty acids which are made up of a much lower percentage of the highly unsaturated acids.

The authors offer the explanation as to the difference in behavior of various oils as follows: Two reactions are involved, one the formation of peroxide from the unsaturated glycerides and the second the oxidation of the vitamin by the peroxide. The division of the oils into two groups corresponds to two different values for the ratio of the rate of peroxide formation to the rate of oxidation of vitamin A by peroxide. Certain factors although they may alter the rates of the two reactions do not affect the ratio so that the division of the oils occurs regardless of their stability. Changes in unsaturation, however, alter the rate of one reaction more than the other and so affect the ratio, which in turn determines whether the oil falls into group I or II. L. F. T.

The Use of Sodium Sulfapyridine by Hypodermoclysis. G. V. Taplin, R. F. Jacox, and J. V. Howland, *J. A. M. A. 114,* 1733 (1940). Sulfapyridine is not universally tolerated when administered orally nor is its absorption from the gastrointestinal tract constant. There is no apparent direct relationship between dosage and blood level of the drug even under controlled intake and output of fluid and weight of patient.

The authors state that solutions of up to 1 per cent. sodium sulfapyridine gave no reactions when injected intracutaneously and subcutaneously.

More than 50 cases of pneumonia and other conditions such as pneumomeningitis, have been treated with sodium sulfapyridine by hypodermoclysis.

The solution is prepared by bringing a physiological salt solution to a boil, allow to cool for five minutes, and then add the powdered drug. Allow to cool to body temperature and administer into the thighs or under the breasts. The initial dosage is 3 to 7 gm. in 1 liter of physiological salt solution dependent upon weight estimated kidney function and state of hydration of patient. The average (tolerated) rate of administration is usually 200 to 300 cc. an hour.

The initial dose may be followed by similar amounts 24 to 36 hours later dependent upon the response of the patient, the blood level attained, and reactions.

The solution of sodium sulfapyridine so prepared is highly alkaline—pH of 10.5 or higher. No untoward reactions due to this factor have been noted.

The advantages of this method over oral administration are:

1. There is no question about absorption, especially when vomiting is present.

2. A concentration in the blood plasma of from 4 to 10 mg. per 100 cc. can be reached within a few hours, and this is maintained for from 18 to 36 hours.

3. The requirement of sodium chloride is supplied at the same time. Many patients dislike taking salt orally.

4. The fluid intake is supplemented. In many cases in which sulfapyridine is given orally it is difficult to maintain fluid intake at optimal levels because of nausea and vomiting.

5. Smaller total doses are generally required.

Sodium sulfapyridine administered by hypodermoclysis also has the following advantages over the intravenous method:

1. There is no danger of local reactions. Five per cent. solutions of sodium sulfapyridine are reported to be very irritating if some of the solution escapes the vein.

2. The effective concentration in the blood is maintained for a longer time—24 hours as compared with about 12 hours.

3. The technic of administration is simpler and more widely applicable.

Ringer's solution was also employed experimentally as a solvent but with it a clear and complete solution could not be prepared.

Toxicity tests revealed no appreciable differences in the incidence of any of the usual reactions to sulfapyridine. M. O. H.

The Use of Dry Tannic Acid in the Treatment of Burns. P. Joly and A. Vadder. *A. dePresse med. 48,* 171 (1940) through *Squibb Abstr. Bull. 13,* 314 (1940). The tannic acid treatment of burns introduced in America in 1925 has become widely adopted in England, Italy, and the U. S. S. R. In France it did not become as popular because of objections to the amount of time and technical difficulties involved in the tanning operations. The authors have simplified the procedure by applying powdered tannic acid directly to the burn and relying on the serous exudate to dissolve the powder. Excellent results were obtained by this method the resultant scars being supple, non-cheloid and very often invisible.

Studies of Two New Substituted Vinyl Barbituric Acids. J. P. Hendrix. *J. Pharmacol. & Exper. Therap. 68,* 22 (1940). The author reports on the pharmacologic study of two selected members of the new series of substituted vinyl barbituric acids, 5-ethyl 5-(1-methyl 1-butenyl) barbituric acid (compound 37) and 5-propyl 5-(1-methyl 1-butenyl) barbituric acid (compound 92) and their actions were compared to those of isoamylethyl barbituric acid.

The compounds are reported to be potent narcotics and the margin of safety in rats and dogs is comparatively wide. The animals receiving approximately minimum anesthetic doses three times weekly for twelve weeks showed no gross or microscopic lesions.

Compound 37 was quite uniform in its action whereas compound 92 showed some evidence of tolerance development. Compound 37 administered to 100 patients in doses of one-half to three grains as a sedative and hypnotic gave good results and no toxic reactions. The action was gradual during induction, relatively brief in duration, and there was a notable absence of after effects following its use.

L. F. T.

BOOK REVIEW

Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.

Embalming Fluids. Simon Mendelsohn, 1940. Published by the Chemical Publishing Co., New York, N. Y. Price: $4.00.

After reading this work the reader was impressed by the constant references to an extensive bibliography throughout the book.

The first chapter on the historical development of embalming is extremely interesting and thought provoking, while the succeeeding material is particularly interesting from a technical standpoint inasmuch as there are chapters on the Chemistry of putrefaction, formulation and production of fluids, chemistry of fluid constituents and the analytical chemistry of the field.

Finally there is a comprehensive study on embalming patents and upon state regulation on embalming fluids which should be of considerable interest to the average person concerned with embalming fluids. Several useful tables are appended.

Despite the fact it is probably too complex for the average embalmer, plaudits are due the author for this well written and useful book which this reader recommends.

NORMAN URANSON.